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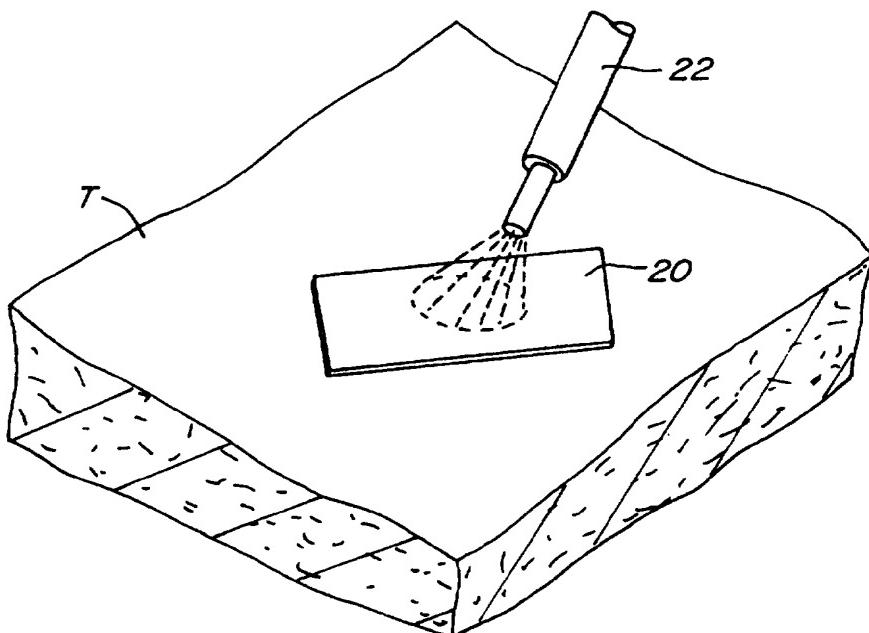
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(54) Title: METHODS AND ARTICLES FOR FUSING POLYSACCHARIDE-CONTAINING MATRIX LAYERS TO TISSUE



(57) Abstract

A matrix material (12) containing a polysaccharide component is fused to tissue (T) by first placing the matrix material (12) over a target location (W) on the tissue (T) and then applying energy to the matrix material (12). The polysaccharide component is of a type and the energy is applied in an amount which together result in fusion of the matrix to the tissue.

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## METHODS AND ARTICLES FOR FUSING POLYSACCHARIDE-CONTAINING MATRIX LAYERS TO TISSUE

### BACKGROUND OF THE INVENTION

#### 1. Field of the Invention

The present invention relates generally to methods and articles for fusing matrix materials to form layers over tissue. More particularly, the present invention relates to fusing polysaccharide-containing matrix layers to tissues for wound closure, and other purposes.

The application and fusing of material layers to tissue is useful for a number of purposes. Of particular interest to the present invention, matrix materials may be applied to tissue in order to effect or enhance wound closure, to augment and repair tissue defects, and the like. A variety of specific compositions and methods have been devised for such purposes. For example, the fusing of collagen and other proteins by the application of laser and other energy sources has been suggested for the closure of wounds. See, for example, U.S. Patent Nos. 5,156,613; 5,209,776; and 5,071,417. The application of pre-polymer materials followed by light-induced cross-linking has also been proposed. See, for example, PCT publications WO 94/24962 and WO 94/21324. The application of other matrix materials without energy as surgery patches has also been proposed. See, for example, U.S. Patent No. 5,201,745. Compositions comprising carboxymethyl-cellulose and hyaluronic acid for placement over tissue to inhibit adhesion and for other purposes. U.S. Patent No. 4,582,865, described the preparation of cross-linked hyaluronic acid gels.

While holding great promise, such methods and compositions for the placement of matrix materials on tissue could be improved in a number of respects. For example, it

would be desirable to provide improved materials which fuse or adhere to the underlying tissue with an enhanced bonding strength upon the application of energy. It would also be desirable to provide materials having enhanced tensile  
5 strength, both before and after the application of energy. Such materials should also possess a degree of elasticity and conformability to enhance positioning and adherence to the underlying tissue, particularly when the tissue undergoes movement which can stress the matrix material. The materials  
10 should further be biocompatible and, at least in some instances, biodegradable so that they can be resorbed or degraded over time.

It would thus be desirable to provide methods and articles for fusing matrix layers to tissue which are improved  
15 in at least one or more of the aspects listed above.

The subject matter of the present application is related to that of the following commonly owned copending applications: USSN 08/303,336 (published as WO 96/07355 on March 14, 1996); USSN 08/481,712 (published as WO 96/07356 on  
20 March 14, 1996); USSN 08/673,710, filed on June 19, 1996; USSN 60/011,898, filed on February 20, 1996; USSN 08/704,852, (Attorney Docket No. 17067-002000), filed on August 27, 1996; and USSN 60/                 (Attorney Docket No. 17067-002100), filed on October 21, 1996. The full disclosures of each of  
25 these applications are incorporated herein by reference.

#### SUMMARY OF THE INVENTION

The present invention provides improved methods and articles for fusing a matrix material to tissue for a variety of purposes, including wound closure, tissue augmentation, or the like. The matrix material comprises a polysaccharide component which when placed over a target location on the tissue will fuse to the tissue upon the application of energy, such as radio frequency energy, laser energy, ultrasonic  
30 energy, heat, infrared, microwave or the like. The energy will be applied in an amount sufficient to fuse the matrix material to the underlying tissue with a peel bond strength of at least about 0.03 N/cm. Thus, as used herein, the terms  
35

"fuse" and "fusing" will mean that the matrix material has been caused to adhere to the underlying tissue with a peel bond strength (defined below) of at least about 0.03N/cm.  
Although the precise energy level will depend on the nature of  
5 the polysaccharide, the nature of the energy source and the nature of the underlying tissue, typically it will be in the range from about 1 W/cm<sup>2</sup> to about 100 W/cm<sup>2</sup>. Exemplary polysaccharides include cellulose derivatives such as hydroxyethyl-cellulose, hydroxy propyl-methyl-cellulose and carboxymethyl-cellulose; glycosaminoglycans such as hyaluronic acid, chondroitin sulfate, chitin and chitosan; starch derivatives such as starch/hydroxyethyl starch; agarose; and alginic acid and combinations thereof. A particularly preferred combination is that of carboxymethyl-cellulose and hyaluronic acid, typically in an equal parts mixture, as described in  
10 WO 96/20349.

The matrix material may be applied (prior to exposure to energy) in a variety of forms, usually being a solid, mesh, or composite layer e.g. a film, usually a thin film having a thickness of at least 0.01 mm, more usually in the range from 0.05 mm to 1 mm. Alternatively, the matrix material may comprise a dispersible, non-solid phase, such as liquids, gels, sols, suspensions, powders, and the like. In some cases, the matrix material may comprise substantially pure polysaccharide(s), but in many cases it will be desirable to combine additional components, such as carrier materials, reinforcement materials, plasticizers, and the like. After the application of energy, a layer of the matrix material will usually fuse to the underlying tissue with the requisite peel bond strength. The layer will typically have a thickness of at least about 0.03 mm, usually being in the range from about 0.05 mm to about 0.1 mm, and the layer will usually form a substantially continuous surface on the underlying tissue. The area may vary widely, typically being at least about 0.05 cm<sup>2</sup>, usually being in the range from about 1 cm<sup>2</sup> to about 100 cm<sup>2</sup>.

In another aspect of the present invention, chitosan and chitin films may be applied to tissue under hydrating

conditions, where the films adhere without the application of energy.

Articles according to the present invention comprise a sheet of the matrix material generally as described above.

5 The sheets will usually be sterilized and present in a sterile package for distribution and storage prior to use.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a perspective view of a sheet of matrix material according to the present invention.

Fig. 2 is a top view of a package containing the matrix material of Fig. 1, shown with a portion broken away.

Fig. 3 is a schematic illustration of a region of tissue having a wound therein.

15 Fig. 4 illustrates the method of the present invention wherein a solid sheet of matrix material is placed over the wound of Fig. 3 and radio frequency (RF) energy is used to fuse the matrix material to the tissue.

Fig. 5 illustrates an alternative embodiment of the 20 method of the present invention, wherein a liquid or gel matrix material is applied using a syringe to the wound in the tissue of Fig. 3.

Fig. 6 illustrates the application of RF energy to the liquid matrix material of Fig. 5.

25 Fig. 7 illustrates a resulting layer of matrix material which has been bonded to tissue according to the method of the present invention.

#### DESCRIPTION OF THE SPECIFIC EMBODIMENTS

30 Methods and articles according to the present invention may be used for fusing matrix materials to tissue for a variety of purposes. Tissues include virtually all human and animal body tissues, including the skin (epidermis), as well as the external and internal surfaces of virtually all body organs. The present invention is particularly useful for fusing matrix materials to fragile body organs, such as lungs, stomach, liver, spleen, intestines, colon, fallopian tubes, esophagus, ovary, uterus, bladder, and the like. The matrix

material may be applied for a variety of purposes, including wound closure, tissue augmentation, and the like. Wounds to be treated may result from accidental trauma, surgical intervention, or virtually any other cause. Tissue 5 augmentation will usually be performed to fill or cover regions of tissue where tissue has been lost or damaged, such as abrasions, burns, and the like.

The matrix materials of the present invention will comprise a polysaccharide component, as described in more 10 detail below. The polysaccharide will be selected to provide for bonding of the resulting layer of matrix material, typically providing a peel bond strength of at least about 0.03 N/cm, preferably at least about 0.07 N/cm, and usually in the range from about 0.07 N/cm to about 0.2 N/cm. Peel bond 15 strength can be measured by conventional techniques. A particular method for measuring peel bond strength is as follows. Pieces of the matrix material (1.5 cm x 3 cm) are cut and glued to a plastic tab (1.5 cm x 3 cm) which overlaps the test material by 1 cm over the width (the 1.5 cm dimension), using a cyanoacrylate glue. A hole is pierced in 20 the tab, and the test material bonded to the tissue *in vivo* or *in vitro*. A digital force gauge, such as an Omega DFO51-2 fitted with a 21 pound force transducer, Omega Instruments, Stamford, Connecticut, is attached to the plastic tab using a hook attachment which is secured to hole in the plastic tab. 25 A manual upward force is then applied on the force gauge, and the sample peeled off with an even rate of pull, typically about 3 cm per second. Peel strengths are recorded in force (Newtons) divided by the width of the sample (1.5 cm) in order 30 to determine the peel bond strength. The peel bond strength is measured as a maximum.

The polysaccharide component may comprise one, two, or more individual polysaccharides. Exemplary polysaccharides include cellulose derivatives such as carboxymethyl-cellulose; 35 hydroxyethyl-cellulose, hydroxy propyl-methyl-cellulose; glycosaminoglycans such as hyaluronic acid, chondroitin sulfate, chitin and chitosan; agarose, and alginate; and starch derivatives such as starch/hydroxyethyl starch.

Preferred polysaccharide materials will include at least a cellulose component, particularly carboxymethyl-cellulose, optionally in combination with a glycosaminoglycan component, such as hyaluronic acid. A particularly preferred material is  
5 a mixture of carboxymethyl-cellulose and hyaluronic acid, typically in equal parts, such as that sold under the tradename SEPRAFILM by Genzyme Corporation.

The polysaccharides may comprise substantially all of the matrix material, or may comprise only a portion  
10 thereof. In the latter case, additional components may be included, such as carrier substances, reinforcing materials (e.g., reinforcing meshes, fibers, filaments, braids and the like), and plasticizers. Exemplary carrier substances include collagen and gelatin.

15 The matrix material will usually be in the form of a solid layer, e.g., in the form of a sheet, film, patch, strip, mesh, or the like. The use of a mesh allows tissue to form a coagulum within the intristices of the mesh as energy is applied, as described in copending application serial no.  
20 08/303,336, the disclosure of which is incorporated herein by reference. As mentioned above, the solid phase forms of the matrix material may optionally be reinforced with filaments, braids, meshes, and other woven and non-woven reinforcement materials. Usually, the reinforcement materials will be non-  
25 bioabsorbable so that they will remain even after the fusible material has been resorbed. Exemplary reinforcement materials include polymeric braids or meshes, particularly composed of polypropylene (Marlex®), fluorinated hydrocarbon polymers (Gore-Tex®), polyesters (such as Dacron®), and the like. In  
30 other cases, the reinforcement materials may be biodegradable. Exemplary biodegradable materials include polylactic acid, polyglycolic acid, copolymers of lactic acid and glycolic acid, polyhydroxybutyrate, other poly ( $\alpha$ -hydroxy acids) polydioxanone, and the like in filaments, braids, meshes,  
35 woven and non-woven forms may be used.

Reinforced and non-reinforced matrix materials may be formed by conventional techniques for forming and solidifying polysaccharides. Usually, the polysaccharides

will be cross-linked to enhance structural integrity. For example, the polysaccharides may be dissolved in water to form a gel. The gel may then be layered over a flat surface to a desired thickness, and the gel dried to form a solid sheet.

5 Such sheets will typically have a thickness in the range from about 0.03 mm to about 0.15 mm, usually from about 0.05 mm to about 0.1 mm. The sheets will preferably have an area of at least about 0.5 cm<sup>2</sup>, preferably at least about 1 cm<sup>2</sup>, and usually in the range from about 1 cm<sup>2</sup> to about 100 cm<sup>2</sup>. It

10 will be appreciated that sheets of various sizes can be trimmed to an appropriate size and shape for a particular application.

Alternatively, the matrix materials may be applied to the target region on the tissue in a non-solid dispersible state, e.g., as a liquid, gel, paste, spray, sol or combination thereof. Such dispersible matrix materials may be applied using syringes, brushes, sprayers, spatulas, or other methods suitable for spreading or dispersing a thin layer of the material over the wound region. Usually, the thin layer will have a thickness in the range from about 0.01 mm to about 5 mm, preferably from about 0.05 mm to about 1 mm.

The method of the present invention will utilize energy of a type and in an amount sufficient to fuse the matrix material including the polysaccharide to underlying tissue. Suitable energy sources include electrical energy, particularly radio frequency (RF) energy, heat energy, laser energy, ultrasonic energy, infrared, microwave, and the like. Preferred are the use of RF energy sources, such as those available as electrosurgical power supplies from companies such as Valleylab, Boulder, Colorado, and Con-Med, Utica, New York, employing conventional RF-applying probes. Particularly preferred are modified RF energy sources which provide for a dispersed or distributed current flow from a hand-held probe to the tissue. One such RF energy source is referred to as a radio frequency inert gas device or inert gas beam coagulator which relies on flow of an inert ionizable gas, such as argon, for conducting current from the probe to the tissue. Such

inert gas beam coagulators are available commercially from suppliers such as Con-Med and Valleylab.

Energy from the energy source is typically directed to the tissue using a probe connected to an external power supply. The treating physician usually directs the probe manually to apply energy over the surface of the matrix material and visually confirms that fusion has been achieved. Using an inert gas beam coagulator an energy output from about 2W to about 100W, preferably from about 20W to about 40W, will be used. The fusible material will typically be exposed to the energy for a total time from about 5 seconds to about 120 seconds, usually from about 10 seconds to about 40 seconds, for material having an area from about 1 cm<sup>2</sup> to about 10 cm<sup>2</sup>. The precise timing depends on the physician's visual assessment that the matrix material has fused to the underlying tissue.

Referring now to Fig. 1, an article 10 comprising a solid sheet 12 of matrix material comprising a polysaccharide component according to the present invention is illustrated. As shown, the sheet is square, but sheets having a variety of other regular and irregular geometries, such as rectangles, circles, ovals, and the like, could also be fabricated. The surface area, thickness, and other characteristics of the sheet 12 are preferably (but not necessarily) as described above.

The solid sheet 12 is usually packaged in a manner suitable to facilitate use by the treating physician. Generally, the sheet material is sterilized and packaged in a suitable container, such as a pouch, box, canister, bottle, or other conventional receptacle for medical products. In Fig. 2, the sheet 12 is illustrated as packaged in a pouch comprising a front sheet 14 and back sheet 16, where the sheets are laminated together around the edge to seal the interior of the package. Alternatively, the sheet material is rolled and packaged in order to provide larger areas of material. Sterilization of the sheet material 12 is accomplished, prior to, during, or after packaging. Suitable sterilization techniques include the use of sterilizing gases,

sterilizing radiation, heat, or the like. Usually, the solid sheet 12 or other form of the material of the present invention will be packaged together with written instructions setting forth the methods described herein, i.e. that the materials are to be placed over a target site in tissue and energy applied to effect bonding. The instructions may be printed on the packaging material (e.g. on a box or on a pouch holding the material) or may be provided on a separate package insert which is placed in or on the product package.

Referring now to Figs. 3 and 4, the use of a strip 20 of the matrix material of the present invention for covering and sealing a wound W in a region of tissue T is illustrated. The strip 20, which has been be trimmed to size prior to use, is placed over the wound W as shown in Fig. 4. After placement of the strip 20, energy such as radio frequency energy is applied over the strip using a hand-held probe 22, as illustrated in Fig. 4. The energy is applied by passing the probe 22 over the upper, exposed surface of the strip to fuse the polysaccharide-containing strip to the underlying tissue. Exemplary power levels, exposure times, and the like, are described above.

Referring now to Figs. 5 and 6, an alternative method for applying matrix material to the wound W on the region of tissue T is illustrated. Liquid or gel matrix material 30 is applied using a syringe 32, typically in a series of parallel strips 34. Other patterns of application, of course, could also be employed, such as circular, spiral, criss-crossed, and the like. It is generally desirable, however, that material be applied at a relatively uniform density over the tissue, so that, after application of energy, a generally continuous layer of matrix material 36 results, as shown in Fig. 6. Again, the energy is typically applied using the hand-held probe 22.

Referring now to Fig. 7, after the application of energy, the matrix material is in the form of a generally continuous layer 40 of material which adheres to the upper surface S of the tissue T. The layer 40 of material will adhere to the tissue T with a minimum peel bond strength as

set forth above. Moreover, the layer 40 will have a relatively high tensile strength so that it can maintain the integrity of the tissue T over the wound W.

5 The following examples are offered by way of illustration, not by way of limitation.

#### **EXPERIMENTAL**

##### Example 1

10 Cross-linked polysaccharide gel materials were prepared from carboxymethyl-cellulose (250 kD), hyaluronic acid, chondroitin sulfate, and chitosan as follows. Each of the polysaccharides was dissolved in 0.2M sodium hydroxide at 4% solids (w/v) to produce a viscous liquid. Divinyl sulfone was rapidly mixed with the viscous liquid to achieve a 0.1% dispersion. A cross-linked gel formed within 1 hour at room 15 temperature, as described in U.S. Patent No. 4,582,865. The gels were washed with 0.3M sodium chloride to remove the sodium hydroxide, and the washed gel was air dried to produce a film. The resulting films had thicknesses from 0.04 mm to 20 0.1 mm.

Non-cross-linked polysaccharide films were cast from 4% (w/v) chitosan solutions in 1% (w/v) aqueous acetic acid and were air dried.

25 The polysaccharide films described above were applied to porcine lung and energy applied as follows. Porcine lung was received on ice from a slaughterhouse, usually within a day of slaughter. The lung was divided at the main bronchus, and one side was used for each test series. A tube was fitted to the largest bronchus, and air was pumped 30 into the lung using a pump (Air Cadet Model 7059-42, Cole-Parmer Instruments, Niles, IL) to achieve inflation. The lung was housed in a chamber of clear acrylic, which was mounted on a heated platform. The air pressure lines were also passed through a heated circulating bath. Heated 0.9% aq. sodium 35 chloride was sprayed on the lung tissue at intervals. Tissue temperatures were maintained between 29° and 40°C, preferably between 37° and 40°C.

Tissue welding with argon beam coagulator and peel strength measurements on porcine lung *in vitro* were performed as follows. Film samples (2 cm x 3 cm) were placed on porcine lung tissue, and the tissue placed in contact with the return electrode of the argon beam coagulator, usually on the underside. Immediately upon placing on the tissue, the film began to hydrate. Welding was preferably performed within 20 sec after placing on tissue, since bonding was a function of film hydration. The spark discharge from the tip of the coagulator was then directed onto a patch at a distance of a few mm between tip and film. The coagulator was typically set at 40 W of power and 2-4 liters/min of argon gas flow. Other settings were explored, but the strength of the bond achieved was less. The spark discharge was maintained for 2-5 sec per  $\text{cm}^2$  of film. Application of the argon spark was terminated when the film became desiccated or showed signs of carbonization.

Peel strength measurements were performed on the films to which polystyrene tabs had been bonded using cyanoacrylate glue (prior to bonding with the argon beam). The polystyrene was approximately 0.5 mm thick, and a hole approximately 4 mm in diameter was punched in the free edge. To measure bonding of the film to the tissue, the tab was hooked (through the hole) to a digital force gauge (Omega model DFG51-2, 2 lb load cell, Omega Engineering, Inc., Stamford, CT). With the patch under no tension, the gauge was set to zero force, and then the gauge was raised manually at a rate of approximately 1 cm/sec to effect a peeling detachment of the film. The gauge was lifted until the film was separated from the tissue. The maximum force registered during the peeling operation was recorded as Newtons of force per cm width of film. Peel strength measurements were typically commenced 3 min after welding to tissue.

The cross-linked carboxymethyl-cellulose films bonded to the tissue with good strength in the range from 0.05 N/cm to 0.1 N/cm. The cross-linked hyaluronic acid, chitosan, and chondroitin sulfate film did not bond.

Cross-linked and non-cross-linked chitosan films initially bonded to the tissue both with and without application of RF energy. Within about 30 minutes, however, both chitosan films became swollen, soft gels with very low cohesive strength.

5           **Example 2**

This study demonstrated the effectiveness of the matrix material containing a polysaccharide component as a wound closure system. The matrix material closed and sealed 10 surgically induced wounds or tissue defects. To demonstrate the efficacy of the matrix material, several wounds were surgically induced in a farm grade Hampshire/Yorkshire cross pig (Pork Power Farms, Turlock, CA).

15           **Animal #1**

Ability of the matrix material to seal to underlying lung tissue.

Following a right side thoracotomy, the lung was exposed. A 2 x 4 cm (approximately 0.05 mm thick) piece of 20 composite material comprising two anionic polysaccharides, sodium hyaluronic acid (11A) and carboxymethyl-cellulose (CMC), Seprafilm™ (Genzyme Corp., Cambridge, MA) was placed on naive lung tissue. Pre-beam apposition was very good. Energy was applied with the ABC 6400 unit (Birtcher Medical Systems, 25 Irvine, California) with settings of 40 watts power and gas flow rate of 4 liters/minute. Three minutes after application of energy and irrigation with saline, the piece was carefully examined and showed good bonding and integrity.

30           **Animal #2**

Ability of the matrix material to seal a surgically induced air leak.

A wedge resection of the lung was performed to expose two bronchioles of ~ 2 mm diameter. Air leak was 35 documented. Four 2 x 4 cm pieces of Seprafilm™ were placed over the resection and leaking bronchiole and attached using an argon beam coagulator. All leaks were sealed when tested by inflating the lung to 25 cm water pressure. The

thoracotomy was closed and air leak measured through a chest tube. Zero flow rate was recorded at 2 minutes 25 seconds i.e. the lung was not leaking and was maintained for 4 hours. Recordings were stopped, chest tube removed and the animal was recovered.

5 **Animal #3**

Ability of the matrix material to seal a surgically induced air leak.

10 The tip of the right lung lower lobe was resected with electrocautery to expose a single 1 mm diameter bronchiole that was leaking. A 2 x 4 cm piece of Seprafilm™ was attached over the leaking bronchiole using an argon beam over the leaking bronchiole. The leak was tested with  
15 irrigation and an inflation challenge. No leak detected at inflation pressure of 43 cm water.

**Animal #4**

The matrix material cannot seal a surgically induced air leak without the application of energy.

20 Using a farm grade Hampshire/Yorkshire cross pig (Pork Power Farms, Turlock, CA) a right side thoracotomy was performed and the lung was exposed. Following the surgical creation of a 2 x 2 cm tissue divot, a 2 x 2 cm piece of Seprafilm™ was placed over the induced divot. No energy was applied to the test matrix. When the lung was hydrated and  
25 inflated, the polysaccharide material moved and air was observed to be leaking through the patch as well as through tunnels between the patch material and the underlying tissue. The material continued to warp and break apart following  
30 additional hydration.

**Example 3**

A comparison of a polysaccharide matrix material with and without the application of energy was performed.

Using a farm grade Hampshire/Yorkshire cross pig (Pork Power  
35 Farms, Turlock, CA) a right side thoracotomy was performed and the lung was exposed. A 2 x 4 cm piece of Seprafilm™ (Genzyme Corp., Cambridge, MA) was placed on naive lung tissue. Using methylene blue tissue stain, a mark was placed around the

perimeter of the 2 x 4 cm piece of Seprafilm". No energy was applied.

Approximately 2 cm away from the site of the "unfixed" Seprafilm an additional 2 x 4 cm piece of Seprafilm was placed on the lung tissue. Energy was applied with the ABC 6400 unit (Birtcher Medical Systems, Irvine, California) with settings of 40 watts power and a gas flow rate of 4 liters/minute.

Both test areas were irrigated with saline. The chest was then closed using surgical clamps. Ten minutes after the chest was clamped closed, the clamps were removed. The "unfixed" patch had shifted approximately 2 cm laterally from the original marked location and exhibited poor integrity. However, the patch which was treated with energy showed good bonding to the underlying tissue.

Although the foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

**WHAT IS CLAIMED IS:**

1        1. A method for fusing a matrix material to  
2 tissue, said method comprising:

3              providing a matrix material containing a  
4 polysaccharide component which binds to tissue upon the  
5 application of energy;

6              placing the matrix material over a target location  
7 on the tissue; and

8              applying energy to the matrix material in an amount  
9 sufficient to fuse the matrix material to the tissue.

1        2. A method as in claim 1, wherein applying energy  
2 to the matrix material results in a layer of material which  
3 fuses to the underlying tissue with a peel bond strength of at  
4 least about 0.03 N/cm.

1        3. A method as in claim 2, wherein the layer has a  
2 substantially continuous surface area of at least about  
3 0.5 cm<sup>2</sup>.

1        4. A method as in claim 1, wherein the layer has a  
2 thickness of at least about 0.01 mm.

1        5. A method as in claim 1, wherein the  
2 polysaccharide is selected from the group consisting of  
3 cellulose derivatives, glycosaminoglycans, starch derivatives,  
4 agarose, and alginate.

1        6. A method as in claim 1, wherein the matrix  
2 material comprises at least a cellulose derivative.

1        7. A method as in claim 6, wherein the matrix  
2 material comprises a carrier substance selected from the group  
3 consisting of collagen or gelatin.

1        8. A method as in claim 1, wherein the matrix  
2 material comprises a solid or mesh layer.

1           9. A method as in claim 1, wherein the matrix  
2 material comprises a dispersible, non-solid phase selected  
3 from the group consisting of liquids, gels, sols, suspensions,  
4 and powders.

1           10. A method as in claim 1, wherein the matrix  
2 material is placed over a wound at the target location in the  
3 tissue to help close the wound.

1           11. A method as in claim 1, wherein the energy is  
2 applied at a level in the range from about 1 W/cm<sup>2</sup> to about  
3 100 W/cm<sup>2</sup> for a time sufficient to fuse the matrix material to  
4 the tissue without a substantial loss of mechanical strength.

1           12. A method as in claim 1 wherein the energy  
2 applying step comprises applying energy from the group  
3 consisting of radio frequency energy, heat energy, laser  
4 energy, microwave, infrared, and ultrasonic energy.

1           13. A method as in claim 12, wherein the energy is  
2 radio frequency energy.

1           14. A method as in claim 13, wherein the energy  
2 applying step comprises directing energy from a radio  
3 frequency inert gas coagulator applicator against the matrix  
4 material at the target location.

1           15. An improved method of the type wherein a matrix  
2 material is fused to tissue upon the application of energy,  
3 wherein the improvement comprises providing a matrix material  
4 including a polysaccharide component which binds to tissue  
5 upon the application of energy.

1           16. An improved method as in claim 15, wherein the  
2 polysaccharide is selected from the group consisting of  
3 glycosaminoglycans, starch derivatives, cellulose derivatives,  
4 agarose, and alginate.

1           17. An improved method as in claim 15, wherein the  
2 matrix material comprises the polysaccharide and a carrier  
3 substance.

1           18. An improved method as in claim 17, wherein the  
2 carrier substance is selected from the group consisting of  
3 collagen and gelatin.

1           19. An improved method as in claim 15, wherein the  
2 matrix material comprises a solid or mesh layer.

1           20. An improved method as in claim 15, wherein the  
2 matrix material comprises a dispersible, non-solid phase  
3 selected from the group consisting of liquids, gels, sols,  
4 suspensions, and powders.

1           21. A tissue closure matrix material for bonding to  
2 tissue upon the application of energy comprising a  
3 polysaccharide component which fuses to tissue upon the  
4 application of energy.

1           22. The material as in claim 21, which binds to the  
2 underlying tissue with a peel bond strength of at least about  
3 0.03 N/cm.

1           23. The material as in claim 21, wherein the sheet  
2 has a substantially continuous surface area of at least about  
3 0.5 cm<sup>2</sup>.

1           24. The material as in claim 21, wherein the sheet  
2 has a thickness of at least about 0.01 mm.

1           25. The material as in claim 21, wherein the  
2 polysaccharide is selected from the group consisting of  
3 glycosaminoglycans, starch derivatives, cellulose derivatives,  
4 agarose, and alginate.

1           26. The material as in claim 21, wherein the matrix  
2 material comprises the polysaccharide and a carrier substance.

1           27. The material as in claim 26, wherein the  
2 carrier substance is selected from the group consisting of  
3 collagen and gelatin.

1           28. A package containing the material of claim 21,  
2 wherein the package is sealed and the article is sterilized  
3 therein.

1           29. The package of claim 28, further comprising  
2 written instructions to place the material over tissue and to  
3 apply energy to the material and tissue to bond the material  
4 to the tissue.

1           30. The material as in claim 21, wherein the matrix  
2 material comprises a solid or mesh layer.

1           31. The material as in claim 21, wherein the matrix  
2 material comprises a dispersible, non-solid phase selected  
3 from the group consisting of liquids, gels, sols, suspensions,  
4 and powders.

1           32. The material as in claim 21, wherein the  
2 polysaccharide component binds with the application of energy  
3 at a level in the range from about 1 W/cm<sup>2</sup> to about 100 W/cm<sup>2</sup>  
4 for a time selected to fuse the matrix material to the tissue.

1           33. The material as in claim 31, wherein the energy  
2 is from a radio frequency inert gas device.

1           34. An article comprising:  
2            a film of a tissue closure material comprising a  
3            polysaccharide component;  
4            a sealed package holding the film, wherein the film  
5            is sterilized therein; and

6               written instructions to place the film over tissue  
7   and to apply energy to the tissue to bond the material to the  
8   tissue.

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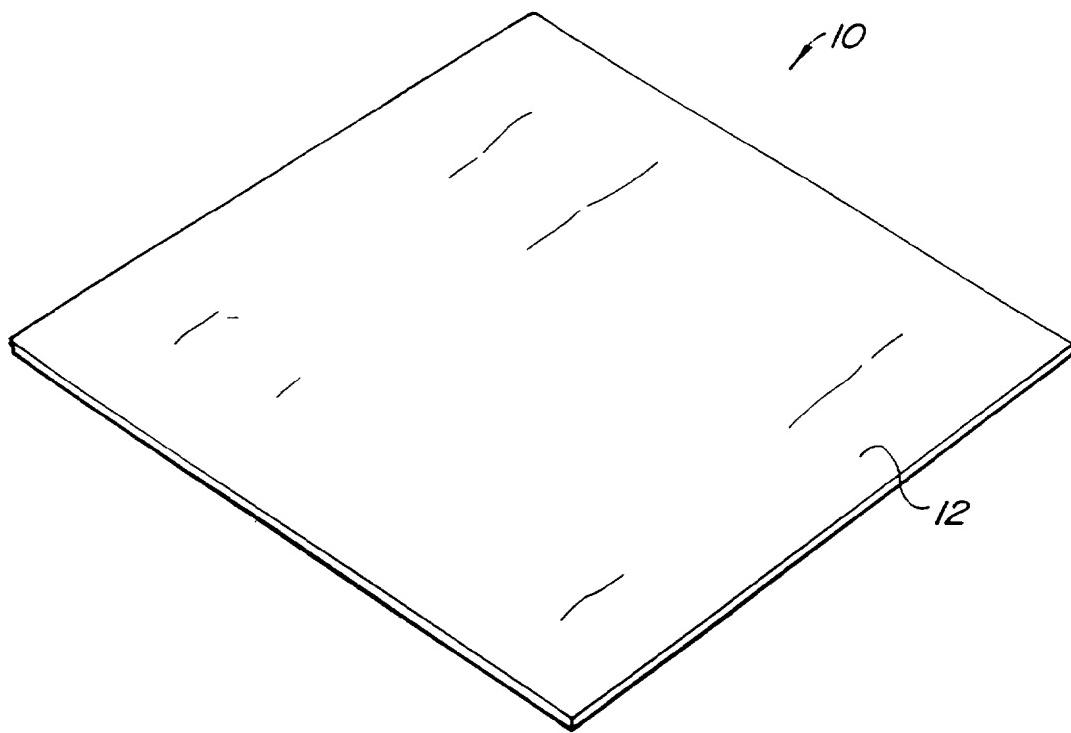


FIG. 1.

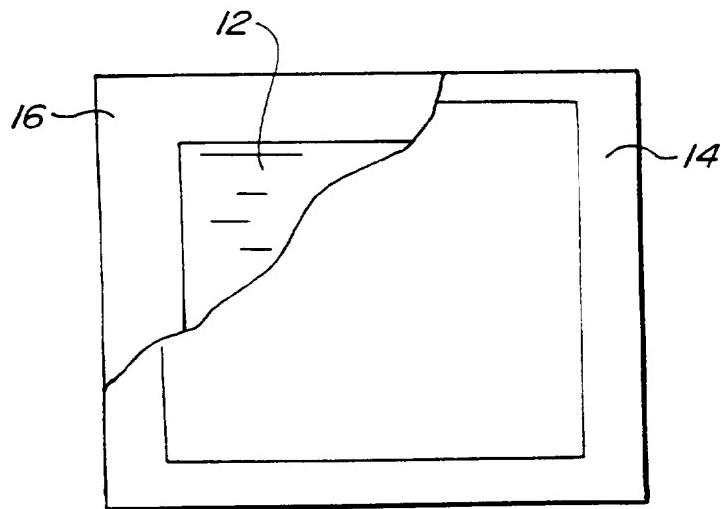
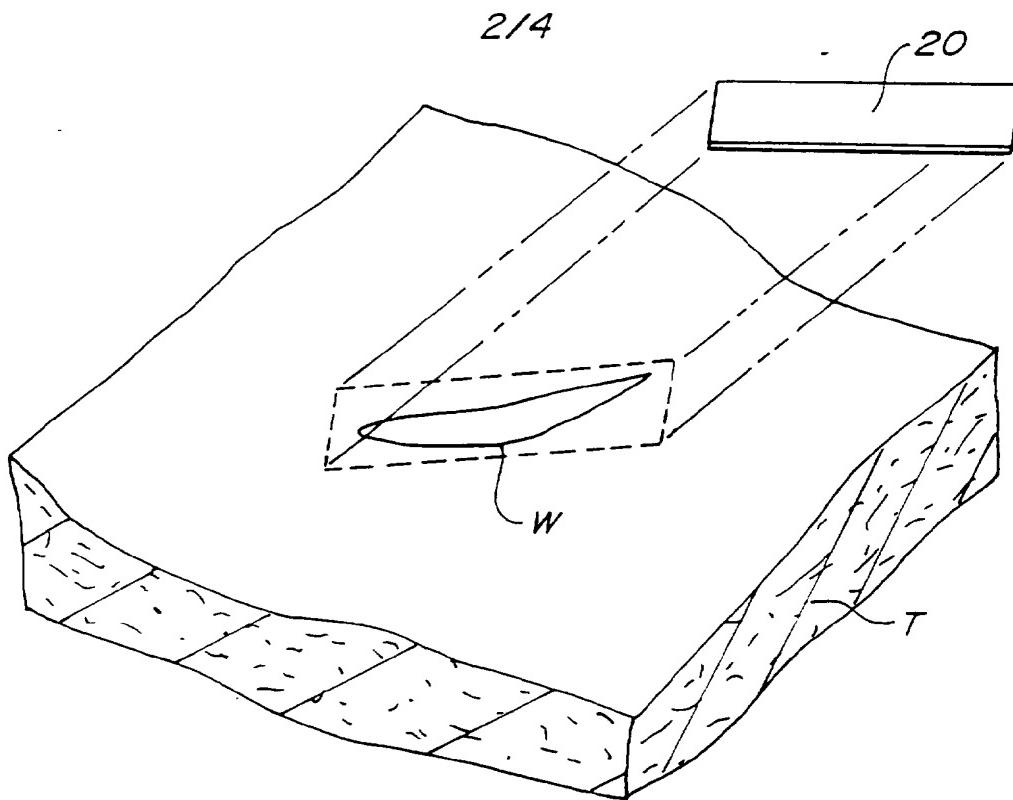
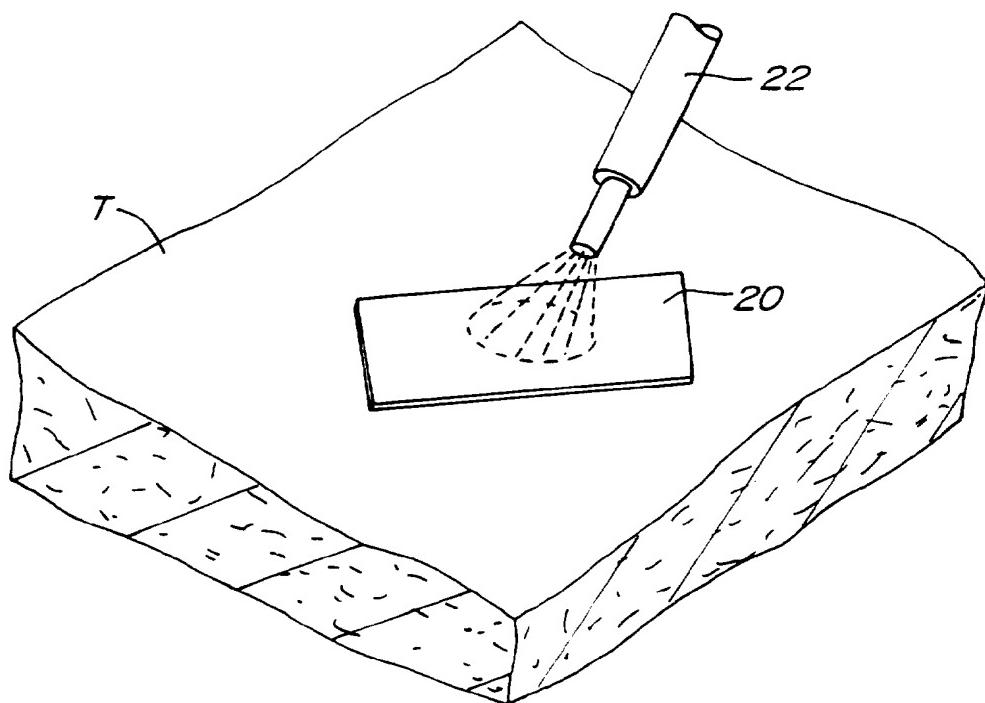


FIG. 2.



*FIG. 3.*



*FIG. 4.*

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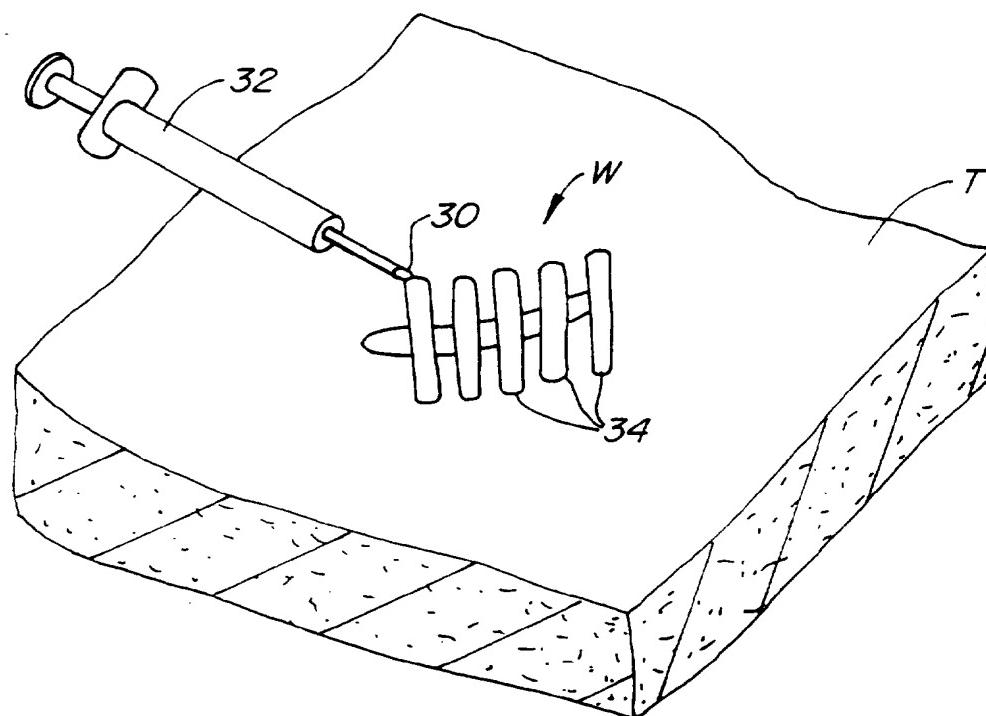


FIG. 5.

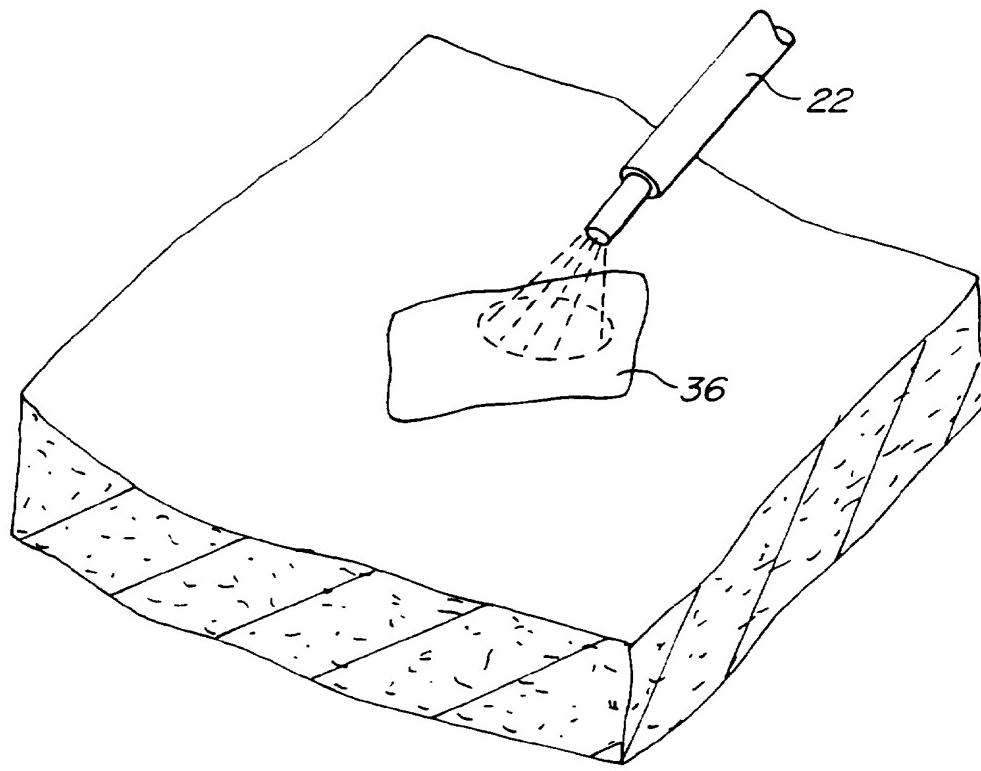
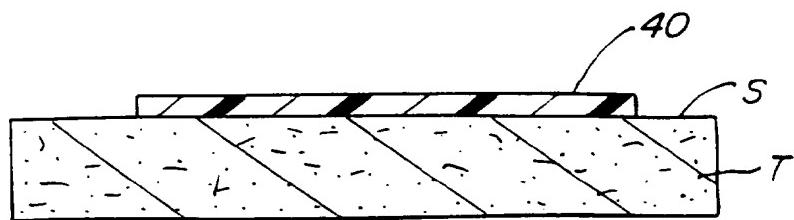


FIG. 6.

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*FIG. 7.*

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/17840

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : A61B 17/08

US CL : 606/213. 214

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 606/213. 214

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --	US 5,209,776 A (Bass et al.) 11 May 1993, col. 4, lines 1-4, lines 33-61, col. 5, lines 2-17, col. 7, lines 50-68, col. 8, lines 1-53.	1, 5-10, 12, 15-21, 25-27, 30-31 -----
Y		11, 13, 28, 32-33
Y	US 5,156,613 A (Sawyer) 20 October 1992, col. 2, lines 56-65, col. 3, lines 37-49, col. 4, lines 1-4.	13, 33
Y	US 3,527,224 A (Rabinowitz) 08 September 1970, col. 2, lines 56-61.	28

Further documents are listed in the continuation of Box C.

See patent family annex.

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